REMARKS

This paper responds to the Office Action mailed July 11, 2003. Prior to entry of this paper, Claims 38, 41-45, and 52-57 were pending in the present Application. In this amendment, Claims 42, 52 and 57 are canceled without prejudice to Applicants' right to pursue the subject matter of the cancelled claims in one or more related applications, while Claims 38, 41, 43-45, and 53-56 are amended. Finally, new Claims 58-60 are presented for examination. Thus, following entry of the present amendment, Claims 38, 41, 43-45, 53-56, and 58-60 will be pending and under consideration.

I. The Amendments to the Claims

The present paper presents amendments to Claims 38, 41, 43-45, and 53-56, and new Claims 58-60. These amendments and new claims are fully supported by the specification and claims of the present application as originally filed. Accordingly, the amendments to Claims 38, 41, 43-45, and 53-56 and new Claims 58-60 do not present new matter.

In particular, support for the amendments to Claims 38, 41, 43-45, and 53-56 may be found, for example, in Claims 38, 41, 43-45, and 53-56, respectively, as originally filed, and in the specification at page 49, lines 19-26, at page 72, lines 26-29, at page 73, lines 9-17, and in the two paragraphs inserted into the specification at page 77 presented at pages 3-5 of the preliminary amendment filed together with the instant application. The Declaration filed in connection with this application acknowledges the amendment as part of the instant application approximately at line 11. Thus, the preliminary amendment is part of the instant application and can be used to support the amendments to the claims. *See* M.P.E.P. § 608.04(b). Additional support for the amendment to Claim 56 may be found, for example, in the specification at page 50, lines 19-24.

Finally, support for new Claims 58-60 may be found, for example, at Figure 1A and in the two paragraphs inserted into the specification at page 77 presented at pages 3-5 of the preliminary amendment filed together with the instant application. Thus, the amendments to the claims and the new claims are fully supported by the specification, claims, and preliminary amendment that was part of the application as filed. Therefore, no new matter is added by way of this amendment. Accordingly, Applicants hereby request entry of the present amendment to the claims under 37 C.F.R. § 1.111.

II. The Amendments to the Specification

The specification has been amended to include four tables, Tables 1-4, inadvertently omitted from the parent application as originally filed. Tables 1-4 are not new matter to the present application. Corresponding tables were filed as Tables 1-4 of parent Application No. 09/874,475 ("the '475 application"). For the PTO's convenience, copies of Tables 1-4 of the '475 application are attached hereto as *Exhibit 1*. In the preliminary amendment filed together with the present application, a sentence was added to the specification claiming priority to and incorporating by reference the '475 application. As noted above, the Declaration for the present application acknowledged the preliminary amendment as part of the application. Therefore, the sentence incorporating the '475 application by reference is part of the present application. Thus, since corresponding Tables 1-4 were part of the '475 application as filed, and the '475 application was incorporated by reference into the present application, Tables 1-4 as presented in the instant amendment are not new matter to the present application. Accordingly, Applicants hereby request entry of the present amendment to the specification under 37 C.F.R. § 1.111.

III. The Objection to the Drawings

The PTO has objected to the drawings currently on file. Revised drawings are attached to this paper as *Appendix A*. Applicants respectfully submit that the revised drawings address the draftsperson's objections presented in the Notice of Draftsperson's Review attached to the Office Action mailed October 3, 2003. Accordingly, Applicants respectfully request withdrawal of the objection to the drawings.

IV. The Indefiniteness Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 42, 45, 52, and 55 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Without agreeing to the propriety of the rejection, Applicants respectfully submit that the rejection of Claims 42 and 52 as indefinite is moot in view of the cancellation of those claims. With respect to Claims 45 and 55, Applicants respectfully submit that one of skill in the art can understand the metes and bounds of those claims. Accordingly, Applicants respectfully submit that Claims 45 and 55 are not indefinite.

In particular, Claims 45 and 55, as amended in the present paper, recite that the plurality of nucleic acids encoding envelope proteins and the viral vector used in the methods of the invention are integrated into the genomes of the cells from the first sample of cells. Thus, nothing in Claim 45 or 55 requires the plurality of nucleic acids encoding envelope

proteins to be part of the same nucleic acid as the viral vector, though they are integrated into the same cell's genome. Therefore, there are no contradictions between Claims 45 and 55 and Claims 38 and 41, from which Claims 45 and 55 depend, and one of skill in the art can understand the scope of Claims 45 and 55. Accordingly, Applicants respectfully submit that Claims 45 and 55 are not indefinite and respectfully request the withdrawal of the rejection of these claims under 35 U.S.C. § 112, second paragraph.

V. The Obviousness Rejection under 35 U.S.C. § 103(a)

Claims 38, 41-45, and 52-56 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Gao *et al.*[1] and/or Petropoulos *et al.*[2] in view of Zhang *et al.*[3] Without agreeing to the propriety of the rejection, Applicants respectfully submit that the rejection is moot in view of the cancellation of Claims 42 and 52 and the amendments to Claims 38, 41, 43-45, 53, 55, and 56. Further, Applicants respectfully submit that the PTO cannot establish *prima facie* obviousness of Claims 38, 41, 43-45, 53-56, and 58-60 as amended in the present paper in view of the cited references, as these references, either alone or in combination, do not teach or suggest each and every element of the invention as presently claimed.

A. *The Legal Standard*

To reject a claim under 35 U.S.C. § 103(a), the PTO bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. *See In re Bell*, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1992). If the PTO cannot establish a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent. *See In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). The PTO must meet a three-part test to render a claimed invention *prima facie* obvious.

To begin with, the prior art references cited by the PTO must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *See In re Kotzab*, 55 U.S.P.Q.2d 1316 (Fed. Cir. 2000). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See id.* Where an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*,

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[1] Gao *et al.*, 1996, *J. Virol.* 70:1651-1667
[2] Petropoulos *et al.*, 2000, *Antimicrob. Agent. Chemother.* 44:920-928
[3] Zhang *et al.*, 1999, *J. Virol.* 73:5225-5230

51U.S.P.Q.2d 1386 (Fed. Cir. 1999). The suggestion may be found in implicit or explicit teachings within the references themselves, from the ordinary knowledge of one skilled in the art, or from the nature of the problem to be solved. *See id.*

Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). The expectation of success, like the motivation to combine two prior art references, must come from the prior art, not the applicant's disclosure. *See id.*

Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See In re Gartside*, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). If any one of these three factors is not met, the PTO has failed to establish a *prima facie* case of obviousness and the applicant is entitled to grant of a patent without making any affirmative showing of non-obviousness.

B. *The Cited References Do Not Teach Each Element of the Claimed Invention*

Claims 38, 41, and 56 each recite a method for detecting the development of an antibody response in a patient infected by an HIV population that is capable of blocking infection. None of the cited references, either alone or in combination, teach or suggest all of the steps of the methods for detecting a neutralizing antibody response recited by Claim 38, 41, or 56.

In particular, Claim 38 recites, *inter alia*, transfecting into a first sample of cells a plurality of nucleic acids, each encoding a viral envelope protein from the HIV population infecting the patient. Claim 41 recites, *inter alia*, incubating a first sample of cells that comprising a plurality of nucleic acids, each encoding a viral envelope protein from the HIV population infecting the patient. Claim 56 recites, *inter alia*, contacting a plurality of viral particles and an antibody preparation with a sample of cells, wherein the plurality of viral particles comprise a plurality of envelope proteins from the HIV population infecting the patient. Neither Gao *et al.*, Zhang *et al.*, nor Petropoulos *et al.* teach or suggest these steps of Claim 38, 41, or 56.

Gao *et al.* teach a single-round virus infectivity assay using individual viral isolates. Whatever the source of the HIV env gene used in these assays (most appear to be from viruses collected to represent potential vaccine evaluation sites), none of the assays tests more than one envelope gene from a single patient. In the assays, nucleic acids corresponding to

the envelope region of HIV were amplified in a PCR reaction, visualized by agarose gel electrophoresis, and cloned into pCRII vectors. *See* Gao *et al.* at page 1652, last full paragraph and paragraph bridging pages 1652-1653. These PCR products were then recloned into pSVIII*env* vectors for use in the single round infectivity assays. *See* Gao *et al.* at page 1654, third full paragraph. Each clone was tested individually for the ability to express a functional envelope protein in the infectivity assay. *See See* Gao *et al.* at page 1654, fourth full paragraph and at Table 2. Thus, Gao *et al.* do not teach a single-round infectivity assay that uses a plurality of nucleic acids, each encoding an envelope protein from an HIV population infecting a patient, or that uses a plurality of viral particles that comprise a plurality of envelope proteins from an HIV population infecting a patient. Further, Gao *et al.* do not suggest that the methods described therein should be modified to use such a plurality of nucleic acids encoding envelope proteins from an HIV population infecting a patient, or to use the proteins encoded thereby, in the single-round infectivity assays. Accordingly, Gao *et al.* do not teach or suggest these elements of the methods of Claims 38, 41, and 56.

Similarly, Zhang *et al.* do not teach or suggest a method for detecting the development of an antibody response capable of blocking infection by HIV that uses a plurality of nucleic acids, each encoding an HIV envelope protein from the HIV population infecting the patient, or the plurality of envelope proteins encoded thereby. Rather , Zhang *et al.* describe a neutralization assay that assess the ability of patient antibodies to neutralize infection by an viral particle that contains a single envelope protein. For example, in Figure 1, Zhang *et al.* illustrate the phylogeny of the *env* clones used in the assays, clearly identifying that each clone represents a single *env* sequence. Zhang *et al.* explain that virual particles containing each of these envelopes were tested for neutralization. *See* Zhang *et al.* at page 5227, Col. 2, first full paragraph. In Figure 3, Zhang *et al.* present the results of these neutralization assays using these single *env* clones. Nowhere do Zhang *et al.* teach or suggest that this assay should be adapted to use a plurality of nucleic acids, each of which encodes an envelope proteins from an HIV population infecting the patient, or to use the plurality of envelope proteins encoded thereby. Accordingly, Zhang *et al.* neither teach nor suggest these elements of Claims 38, 41, and 56.

These deficiencies of Gao *et al.* and Zhang *et al.* are not remedied by Petropoulos *et al.* As noted by the PTO, "Petropoulos *et al.* do not teach analyzing a patient-derived *env* segment for their ability to infect new cells and for compounds that may inhibit virus entry." *See* Office Action mailed October 3, 2003, at page 5. If Petropoulos *et al.* do not teach

analyzing a patient-derived *env* segment for its ability to infect new cells, it is not clear to Applicants how Petropoulos *et al.* could teach or suggest a method that uses a plurality of *env* segments from an HIV population infecting a patient, or that uses a plurality of envelope proteins encoded thereby. Accordingly, Applicants respectfully submit that Petropoulos *et al.*, like Gao *et al.*, do not teach or suggest these elements of Claims 38, 41, and 56.

In view of the foregoing, Applicants respectfully submit that none of Gao *et al.*, Petropoulous *et al.*, and Zhang *et al.*, either alone or in combination, teach or suggest a method for detecting the development of an antibody response in a patient infected by an HIV population that is capable of blocking infection that uses a plurality of nucleic acids, each encoding an envelope protein from the HIV population infecting the patient, or that uses the envelope proteins encoded thereby, as recited by Claim 38, 41, or 56. Therefore, Applicants respectfully submit that the cited references do not teach each and every element of Claims 38, 41, and 56, and thus the PTO cannot establish *prima facie* obviousness of these claims. Because each of the remaining claims depends from one of Claims 38, 41, or 56, Applicants respectfully submit that the PTO cannot establish *prima facie* obviousness of Claims 43-45, 53-55, and 58-60 as well. Accordingly, Applicants respectfully submit that Claims 38, 41, 43-45, 53-56, and 58-60 are not obvious under 35 U.S.C. § 103(a) and earnestly request the withdrawal of the outstanding rejection on this basis.

CONCLUSION

Applicants believe that claims 38, 41, 43-45, 53-56, and 58-60 satisfy all the criteria for patentability and are in condition for allowance. An early indication of the same and passage of the claims to issuance is therefore kindly solicited.

No fee in addition to the Extension fee is believed due in connection with this response. However, the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. § 1.17 and all required extension of time fees, or credit any overpayment, to Jones

Day U.S. Deposit Account No. 503013 (order no. 101962-999007). A copy of this sheet is enclosed.

Respectfully submitted,

Date: April 2, 2004

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